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Caffeine disposition in obesity

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1 Caffeine pharmacokinetics were studied in 16 obese (mean ± s.e. mean body weight; 110 ± 8 kg; % ideal body weight (IBW); 186 ± 14%) and 23 normal body weight (64 ± 3 kg; 103 ± 3% IBW) subjects. Eight obese and four control subjects were cigarette smokers. After abstaining from caffeine for 48 h and an overnight fast, each subject ingested 162 mg caffeine orally. Concentrations of caffeine were measured in plasma samples obtained during the 24 h following the dose and pharmacokinetic variables were determined.

2 The apparent volume of distribution was increased markedly in obese subjects (69.9 ± 5.9 *vs* 43.6 ± 2.8 l; $P < 0.001$) in the absence of any change in oral clearance (135 ± 14-obese *vs* 112 ± 12 ml/min; NS), resulting in a trend toward increased elimination half-life (7.05 ± 1.08-obese *vs* 5.40 ± 0.40 h; NS).

3 Apparent volume of distribution correlated well with percent IBW ($r = 0.65$; $P < 0.001$). Caffeine clearance, suggested as a measure of *in vivo* cytochrome P-448 activity in humans, was not altered in obesity. In contrast, the extent of caffeine distribution increased in direct relation to body weight.

4 If caffeine is used therapeutically, the loading dose should be calculated as a function of total body weight. Since clearance of caffeine is not related to body weight, these data indicate that a chronic dosing regimen to maintain a given plasma caffeine concentration should not be altered due to obesity.

Keywords caffeine obesity pharmacokinetics

Introduction

Caffeine, perhaps the most extensively consumed xenobiotic in the world (Greden, 1979; Levi, 1967; Ritchie, 1975), has received increasing attention as a therapeutic agent for the treatment of bronchospastic disease and neonatal apnoea (Aranda *et al.*, 1977, 1979; Becker *et al.*, 1984). Previous human studies of caffeine disposition in man have focused on factors which govern its metabolic biotransformation and clearance (Blanchard & Sawers, 1983a,b; Brazier *et al.*, 1983; Broughton & Rogers, 1981; Desmond *et al.*, 1980; Knutti *et al.*, 1981; Mitchell *et al.*, 1983; Newton *et al.*, 1981). These studies indicate that caffeine undergoes hepatic oxidation to a variety of biologically active methylxanthine products and that caffeine clearance may be closely related to cytochrome P-448 (P_1-450) activity in the human (Aldridge & Neims, 1979; Aldridge *et al.*, 1977; Grant *et al.*, 1983; Weitholtz *et al.*, 1981). In addition, formation of one metabolite (5-acetylamino-6-formylamino-3-methyluracil) exhibits acetylation polymorphism that parallels acetylator phenotype (Grant *et al.*, 1983). To date, however, little attention has

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been given to changes in the distribution of caffeine which may occur in different populations.

Previous studies have shown that, in the absence of other diseases, obesity may prolong dramatically the elimination half-life of some drugs such as thiopentone (Jung *et al.*, 1982), diazepam (Abernethy *et al.*, 1981) and phenytoin (Abernethy & Greenblatt, 1983) owing to markedly increased distribution with no change in drug clearance. The therapeutic consequence is prolongation of the time required to reach steady-state drug concentrations during chronic dosing unless a loading regimen is employed and a prolonged time for drug washout after cessation of chronic dosing (Abernethy *et al.*, 1983). In such a circumstance a loading dose may require adjustment on the basis of body weight.

We report the effect of obesity on caffeine distribution and clearance.

Methods

Subjects

Sixteen obese (11 women, five men: all weighing more than 125% of ideal body weight (IBW) and with body mass index (BMI) greater than 25.7) and 23 normal body weight individuals (16 women, seven men: all weighing less than 125% IBW and with BMI less than 26.7) participated in the study after giving written informed consent for the protocol which was approved by the local ethics committee. For all subjects physical examination revealed no abnormalities with the exception of obesity, and results of laboratory screening, including liver function tests and serum creatinine were normal. Subjects were taking no medication and were not on special diets designed for weight loss. Eight obese and five control subjects were cigarette smokers.

IBW was defined from life insurance tables as follows (Anon, 1959):

IBW (men) = 110 pounds ± 5 pounds per inch above or below 5 ft height
IBW (women): = 100 pounds ± 5 pounds per inch above or below 5 ft height

BMI was defined as: BMI = body weight (kg)/ height in square metres (Baecke *et al.*, 1982; Frisancho & Fiegel, 1982).

Percent IBW was calculated as the ratio of actual or total body weight (TBW) to IBW.

Procedure

All subjects were asked to abstain from caffeine consumption 48 h prior to the study. After fasting overnight, each subject ingested 325 mg citrated caffeine (Lilly) with 100 ml water (equivalent to 162 mg caffeine). Subjects continued to fast for 3 h after drug administration. Venous blood samples were drawn from an indwelling butterfly cannula kept patent by flushing with 0.5 ml of a 10 u/ml heparin solution during the first 10 h after the dose, and by venepuncture at 24 h. Samples were drawn into heparinized tubes before the dose and at 5, 10, 15, 30, 45 min, 1 h, 2, 3, 4, 6, 8, 10 and 24 h after drug administration. Plasma was separated and stored at −20°C until assayed for caffeine concentration.

Concentrations of caffeine in all plasma samples were determined by high-pressure liquid chromatography using UV detection at 280 nm wavelength by the method of Blanchard *et al.* (1980). The internal standard was phenacetin. The analytical instrument was a Waters model 6000A pump with a reverse-phase C-18 microbondapack column and a Waters model 440 UV absorbance detector fitted with a 280 nm wavelength filter. The mobile phase was acetonitrile 25% (v/v): aqueous buffer (0.01 M acetate—pH 4.0) 75% (v/v) run at a flow rate of 1.8 ml/min. The sensitivity of this method for caffeine was 0.05 μg/ml, and variation between replicate samples was less than 5%. The retention time for caffeine was 10.25 min and for phenacetin it was 7.5 min. No interfering peaks from endogenous plasma constituents or caffeine metabolites were detected.

Pharmacokinetic parameters for caffeine were determined using previously described methods (Abernethy *et al.*, 1984; Gibaldi & Perrier, 1975; Wagner, 1975). The slope of the terminal phase of the plasma drug concentration curve was used to calculate the elimination half-life (Figure 1). The area under the plasma drug concentration curve from time zero until the final measured plasma concentration was determined by the trapezoidal method. To this was added the residual area extrapolated to infinity, calculated as the final concentration divided by the rate constant describing the terminal elimination phase yielding the total area under the plasma concentration curve from time zero to infinity (AUC). Clearance was calculated as dose divided by AUC, assuming complete systemic availability of caffeine after oral administration (Blanchard & Sawers, 1983b). An apparent volume of distribution was calculated as clearance divided by the elimination rate constant. Owing to the limited extent of caffeine binding to plasma proteins (35%), pharmacokinetic parameters based on unbound drug concentrations were not calculated.

Differences between obese and normal body weight subjects were determined by the unpaired

Student's *t*-test. Since subjects were not well matched for cigarette smoking, contribution of this variable was evaluated by analysis of covariance, and the identified subgroups analyzed by analysis of variance.

Results

Plasma caffeine concentrations were well described by a rapid rate of absorption followed by monoexponential elimination (Figure 1). Age and sex were closely matched between obese and control groups, however cigarette smokers were overrepresented in the obese group (Table 1). The degree of obesity, measured as percent IBW, indicated that obese subjects were nearly twice their predicted IBW (Table 1). A comparison of percent IBW to another widely used anthropometric measure of obesity, BMI, showed that the two measures were highly correlated in this population ($r = 0.99$). The elimination half-life of caffeine tended to be greater in obese subjects, although this difference did not reach statistical significance (Table 1, Figure 2). This was the result of a marked increase in apparent volume of distribution with no change in oral clearance (Table 1, Figure 2). Stratification of groups between smokers and non-smokers, or evaluation of non-smokers only did not change this finding. Analysis of covariance for the contribution of smoking indicated that among all subjects, smokers had higher clearance than non-smokers ($P < 0.02$). However, subgroup analysis (by analysis of variance) indicated no significant differences in clearance between obese and control non-smokers or obese and control smokers. Analysis of covariance indicated smoking did not contribute significantly to overall variance in apparent volume of distribution. Correction of apparent volume of distribution

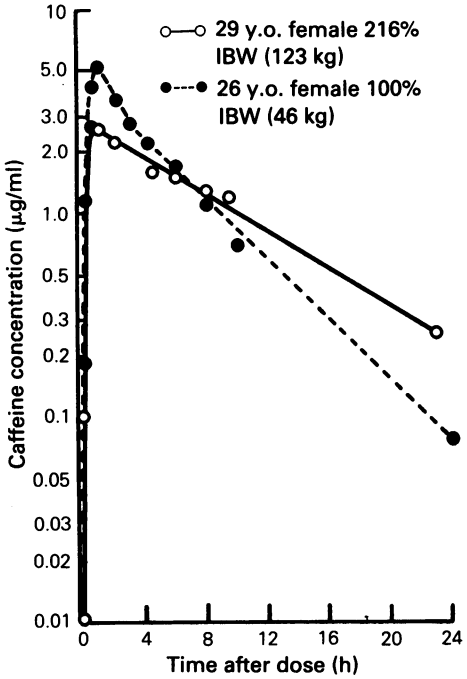

Figure 1 Plasma caffeine concentrations after oral caffeine administration to representative obese (o) and normal (•) body weight non-smoking subjects.

Table 1 Subject characteristics and kinetic variables for caffeine in obese and control subjects (mean ± s.e. mean)

	Mean ± s.e.	
	Obese	*Control*
Subject characteristics		
Number	16	23
Age (years)	32 ± 2	28 ± 1
Weight (kg)	109 ± 8	64 ± 3*
Percent ideal body weight	186 ± 14	103 ± 3*
Body mass index (wt/ht^2)	39.1 ± 2.8	22.0 ± 0.6*
Sex (M/F)	5/11	7/16
Cigarette smokers	8	5
Kinetic variables		
Elimination half-life (h)	7.05 ± 1.08	5.40 ± 0.48
Apparent volume of distribution (l)	69.9 ± 5.9	43.6 ± 2.8*
Apparent volume of distribution per kg body weight (l/kg)	0.653 ± 0.044	0.689 ± 0.041
Oral clearance (ml/min)	135 ± 14	112 ± 12

*$P < 0.001$ by unpaired Student's *t*-test

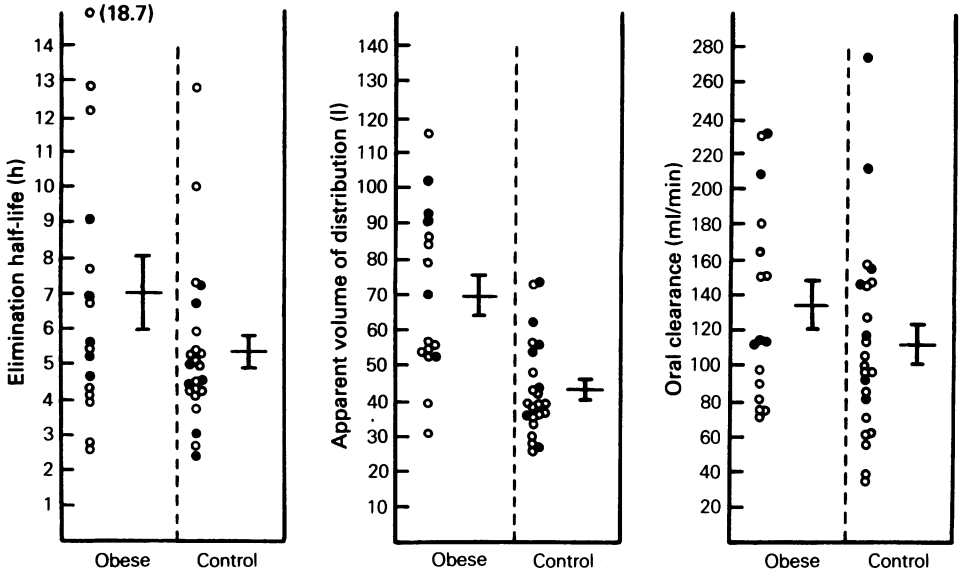

Figure 2 Elimination half-life apparent volume of distribution and oral clearance of caffeine in obese and control subjects. • males, ○ females.

for body weight indicated no difference between obese and control subjects (Table 1). This suggests that the distribution of caffeine into excess body weight over IBW occurs to the same extent as distribution into IBW. Percent IBW, used as a measure of adiposity, was highly correlated with apparent volume of distribution, but was not related to oral clearance (Figure 3).

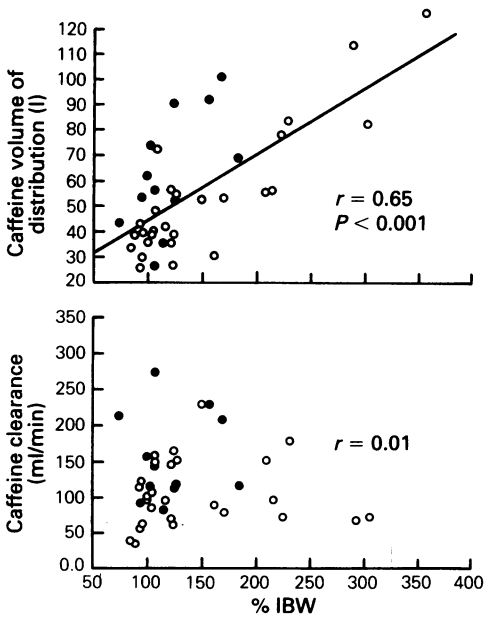

Figure 3 Relationship of percent ideal body weight (IBW) to caffeine volume of distribution and to oral clearance. • males, ○ females.

Discussion

These findings indicate that caffeine distribution in obese subjects increases in parallel with the degree of obesity in the subject. A lack of change in caffeine clearance associated with obesity confirms previous findings with antipyrine, diazepam (Abernethy *et al.*, 1981), and alprazolam (Abernethy *et al.*, 1984), in which hepatically oxidized low clearance drugs did not show altered clearance in obese subjects. In addition, if caffeine is a useful marker for cytochrome P-448 (P_1-450) activity (Weitholtz *et al.*, 1981), these data suggest that obesity is not associated with *in vivo* changes in this enzymatic activity.

The increase in caffeine distribution in obese subjects is similar to that reported for another methylxanthine, theophylline (Gal *et al.*, 1978; Jusko *et al.*, 1978; Rohrbaugh *et al.*, 1982). The physiological basis for such an increase in distribution volume *in vivo* must be related to an increase in the size of one or more of the physiologic compartments into which caffeine distributes. Adipose tissue represents the most obviously increased tissue in the obese population. The octanol:water partition coefficient for caffeine is $P = 0.85$ (Leo *et al.*, 1971). This distribution ratio is similar to that for theophyl-

line (P = 0.96) (Leo *et al.*, 1971). However, increased distribution into nonadipose tissues must also be considered, since lean body mass and total body water are also increased in obese subjects (Forbes & Welle, 1983).

When caffeine is used clinically in the treatment of bronchospastic disease, to attain similar initial plasma concentrations among patients with varying degrees of obesity, loading doses should be calculated as a function of total body weight since the loading dose is a simple multiple of body weight. Since caffeine clearance is not different in obese and normal body weight subjects, maintenance doses may be calculated independent of weight.

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